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Melanoma after laser therapy of pigmented lesions - circumstances and outcome

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Abstract: The use of laser therapy in the treatment of pigmented lesions is a controversial issue as it can delay melanoma diagnosis and may negatively impact mortality. Few cases of melanoma after laser therapy have been reported. It is still unknown whether melanoma can be induced by lasers. We discuss the outcomes of twelve patients presenting with melanoma subsequent to previous treatment with laser. In four patients, a skin biopsy was performed before laser treatment. Histology was re-evaluated by a panel of experienced dermatopathologists and analyzed in the context of clinical and photo-optical data. There was evidence for pathological misdiagnosis in two cases. The other two cases initially presented with non-suspicious features before laser treatment and were clearly diagnosed as melanoma thereafter, opening the possibility of melanoma induction by laser treatment. Most patients were female and presented with facial lesions. Three patients have already died of melanoma and two are in stage IV, showing progressive disease with distant metastases. Laser therapy is a common treatment for pigmented lesions, increasing the risk of delayed melanoma diagnosis. This prevents appropriate and timely therapy, and may therefore lead to a fatal outcome. A careful examination of all pigmented lesions using surface microscopy and representative biopsies in combination with a close follow-up is recommended.

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Title page

(1) Melanoma after Laser Therapy of Pigmented Lesions – Circumstances and Outcome

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Abstract

Use of laser therapy in the treatment of pigmented lesions is a controversial issue, as it can delay melanoma diagnosis and may negatively impact mortality. Few cases of melanoma after laser therapy have been reported. It is still unknown whether melanoma can be induced by lasers.

We discuss the outcomes of twelve patients presenting with melanoma subsequent to previous treatment with laser.

In four patients, skin biopsy was performed before laser treatment. Histology was re-evaluated by a panel of experienced dermatopathologists and analyzed in the context of clinical and photo-optical data. There was evidence for pathological misdiagnosis in two cases. The other two cases initially presented with non-suspicious features before laser treatment and were clearly diagnosed as melanoma thereafter, opening the possibility of melanoma induction by laser treatment. Most patients were female and presented with facial lesions. Three patients have already died of melanoma and two are in stage IV, showing progressive disease with distant metastases.

Laser therapy is a common treatment for pigmented lesions, increasing the risk of delayed melanoma diagnosis. This prevents appropriate and timely therapy, and may therefore lead to a fatal outcome. A careful examination of all pigmented lesions using surface microscopy and representative biopsies in combination with a close follow-up is recommended.

Keywords: Lasers; Lentigo maligna; Melanoma; Naevus; Naevus, pigmented

Introduction

Now that the basic principles of laser surgery have been established, various chromophores, e.g. melanin, can be targeted effectively with minimal injury to surrounding structures [1]. Today, lasers are successfully applied in the treatment of many medical conditions, preferentially in easily accessible organs such as the skin. There has been a notable and substantial increase in the number of applications of laser or similar devices in the western world; this is not restricted to physicians and can involve cosmetologists and aestheticians, for example. Melanin-specific, high-energy, quality-switched (QS) laser systems are able to lighten or eradicate epidermal and dermal pigmented lesions [2]. Nonetheless, the appropriateness of laser use in the treatment of melanocytic lesions continues to be debated. The incidence of melanoma is still rising in Caucasian populations [3], but early diagnosis is responsible for a plateau in melanoma mortality [4]. Laser therapy can delay melanoma diagnosis and may negatively impact mortality [5].

This study identified 12 patients treated with laser and diagnosed with melanoma thereafter. Most patients were female and presented with facial lesions. In four cases, biopsies prior to laser treatment were available. There was evidence for pathological misdiagnosis in two cases that showed malignancy on re-evaluation. The other two cases presented with non-suspicious features before laser treatment and were clearly diagnosed as melanoma thereafter, introducing the possibility of induction of melanoma by lasers.

As only few cases of melanoma subsequent to previous treatment with laser have been reported, it is likely that our sample of 12 patients represents an underestimated medical problem that requires urgent attention from the medical community.

Patients and methods

From 1999 until 2007, all patients with melanoma and a history of laser treatment who presented at the University Hospital of Zurich were evaluated. This study used patient records to investigate melanoma development, outcome, and the time from laser treatment

to melanoma diagnosis. All histology was re-evaluated by a panel of experienced dermatopathologists and analyzed in the context of clinical and photo-optical data.

Study Population

Of the 12 patients studied, nine were female. The mean age was 55.08 years at the time of melanoma diagnosis. In four cases, a nodular malignant melanoma (NMM) occurred; four patients presented with lentigo maligna (LM) or lentigo maligna melanoma (LMM) and four with other melanoma types. Ten of the treated lesions were located on the face; the other two were located in the upper extremities (Table 1). Ablative lasers were used for all patients included in this sample, whereas, in cases from the literature, lesions were also treated with pigment-specific lasers.

For the three patients who were already described in reports from 1999 and 2003 [5,6] an update is provided.

Literature review

A Pubmed literature review was performed using the words ‘melanoma, laser’ and ‘laser, pigmented lesion’ from 1986 to 2007. Identified articles were analyzed with special interest paid to patient histories, in order to identify the circumstances and the delay of melanoma diagnosis [5-16].

Results

In eight patients from our sample and five cases from the literature, no initial histological evaluation was performed prior to laser treatment [8,9,12,13]. Among them was the patient discussed in 1999 [5], who died of metastatic disease with pulmonary, cerebral, dermal, and abdominal metastases 84.33 months after laser therapy.

Biopsies were performed before laser therapy in four patients from our sample [6] and in one case from the literature [8]; these were histologically diagnosed as non-suspicious and subsequently followed by laser treatment. In two of the cases from our retrospective sample

and in the case from the literature, histological re-evaluation of the biopsies after melanoma diagnosis identified a malignant process. In the other two patients from our retrospective sample, biopsies were considered non-suspicious even though sample size and quality were limited and possibly not appropriate for a reliable diagnosis [6]. One of those, the patient described in 2003 showed a nodular melanoma five years after the initial shave-biopsy of a benign melanocytic naevus, which was retrospectively confirmed as benign. This patient developed multiple intrapulmonary, soft tissue and brain metastases [6].

In one patient from our sample and three cases from the literature, lentigo maligna was treated with laser [7,12,14].

Case studies

Case 1

A 52-year-old female patient presented to us in 2003 with a newly diagnosed, unclassifiable malignant melanoma on her right cheek (Fig. 1C and 1D). Breslow's index was 2.6 mm, the Clark level was IV, and the sentinel node biopsy was negative. The medical history revealed several carbon dioxide- (CO₂ -) and erbium-laser treatments of the lesion over the past six years. The lesion had existed since mid-1996 and was clinically diagnosed as a seborrheic keratosis by a dermatologist in 1997. After the third laser treatment, a biopsy of the relapse was performed with a histological diagnosis of a junctional melanocytic naevus. The initial histological diagnosis was reviewed retrospectively and confirmed by a panel of experienced dermatopathologists, although the sample size and quality were limited (Fig. 1A and 1B). The patient now participates in our constant aftercare with no sign of metastasis and stage IIA disease (T3aN0M0).

Case 2

A 72-year-old male patient first presented to us in 2006 with several histologically confirmed dermal satellite metastases on his forehead (Fig. 2D). Six months earlier, a lentigo maligna

with conversion to lentigo maligna melanoma was diagnosed with a Breslow's index of 2.8 mm and a Clark level of V. Sentinel lymph node was negative.

Two years earlier, a pigmented skin lesion considered to be a melanocytic naevus (Fig. 2A) was excised from the same location with external pathological diagnosis of melanocytic naevus with moderate atypia. After this diagnosis, the lesion was treated with laser. Despite the limited sample size and quality, re-evaluation by a panel of experienced dermatopathologists after the melanoma diagnosis revealed atypical melanocytes over actinically damaged skin that was considered to be melanoma *in situ* (Fig. 2B and 2C).

Pulmonary metastases during treatment with dacarbazine and a progressive course of cerebral metastases under vindesine and interferon alfa-2a led to the patient's death.

Outcome

In our patients, we observed a time from laser treatment to melanoma diagnosis ranging from 5.75 to 84 months, with a mean time of 33.33 months (Table 1). The interval between first excision with diagnosis of a benign process and excision of a melanoma ranged between 1.84 and 135.68 months. From first appearance of the skin lesion to laser therapy, 1 to 132 months passed. In one patient, a lesion at this location had existed since childhood.

The diseases of seven patients are in complete remission. Two patients are in stage IV, showing distant metastases at follow-up. The survival of these patients (first distant metastasis to follow-up) is 60 and 75 months. Three patients have already died from melanoma with survival times (first distant metastasis to death) of 9, 20 and 22 months.

Cases in the literature

The 12 patients published in the literature with melanoma subsequent to previous treatment with laser were treated with QS-ruby laser or with ablative devices [5-16]. Likewise to our findings, with ablative laser treated patients only, the average interval between laser treatment and melanoma excision was 36.1 months. The time from first excision to diagnosis

of malignant melanoma ranged from 18 to 144 months (data not shown). The interval from first appearance of skin lesions to laser therapy was only described for three patients in the literature: 120 months for two patients [8,14], and 72 months for another patient [13]. Follow-up data were rarely assessed in the literature, and in half of the cases, no clinical outcome was mentioned.

Discussion

Based on our observations, together with published information, we assume a biologically relevant delay in melanoma diagnosis due to laser treatment, retarding appropriate staging and therapy. The circumstances of the cases are varied.

Clinical misdiagnosis

When laser treatment is performed without any initial histological evaluation, a clinical misdiagnosis can be assumed since every 200th pigmented lesion excised as a melanocytic naevus turns out to be a malignant melanoma [9]. Three-quarters of lesions in people without preserved biopsy specimens were located on the face (10/13), and two-thirds (9/13) were in female patients [5,8,9,12,13]. It can therefore be assumed that laser treatment was chosen for aesthetic reasons. The widespread use of lasers for this purpose is alarming [17], considering the fatal outcome in two of these patients.

Histological misdiagnosis

Determination of initially non-suspicious histological findings as malignant upon re-evaluation might be due to limited sampling. Laser therapy is only indicated in selective cases and only after collection and preservation of histological specimens [8]. However, limited sampling might be inadequate for accurate histological diagnosis of pigmented melanocytic lesions on actinically damaged skin [11,18]. Thus, it remains unclear whether punch and shave biopsy techniques are sufficient to rule out malignancy [18].

Benign process before laser treatment

There are several possible explanations for melanoma development in patients who had a histological diagnosis of a benign process before melanoma excision, including the possibility of melanoma induction by lasers.

The laser treatment may have been inadequate for destruction of the entire lesion [13]. Superficial biopsies are suboptimal, as the boundaries of deep margins cannot be fully ascertained [19]. Areas chosen for biopsy may fail to reveal the foci of invasive melanoma within a lesion [18]. Deeper intrafollicular melanocytes may not receive sufficient energy when treated with QS-laser systems, thus allowing for recurrence [13]. Ablative systems such CO₂ and argon lasers are not pigment-specific and carry a special risk of relapse [20]. In our series, all patients were treated with ablative laser devices. Incomplete surgical removal [21] as well as laser treatment [22] of benign melanocytic naevi may result in histological features of so-called pseudo-melanoma. Such recurrent pigmented lesions clinically as well as histologically resemble superficially spreading melanoma. Even histology may not always distinguish malignant from benign in those cases.

To date, there has been no directly demonstrated correlation between laser treatment and malignant transformation of dysplastic naevi [23]. Helium-neon laser treatment leads to proliferation in melanoma cells [24]. Sub-lethal laser damage to melanoma cells led to an increased p16 level, implying that DNA damage had taken place [25]. Relapse of congenital naevi after QS-alexandrite-laser treatment might be due to proliferation of melanocytes after down-regulation of E-cadherin and TNF-alpha [26]. It remains unclear whether QS-ruby lasers (QSRL) are able to transform benign melanocytes into malignant ones [13]. Hafner and co-workers investigated the impact of QSRL on primary melanocytes and showed that laser treatment does not result in major alterations of global gene expression, particularly in genes associated with melanoma [27].

Lentigo maligna treated with laser

Lentigo maligna (LM) is an *in situ* melanoma in UV-damaged skin of patients with advanced age. The clinical hallmark of LM is very slow but steady and continuous horizontal expansion of atypical melanocytes which tend to diverge into subclones. These subclones can be identified by pigmentation changes which give the lesion a heterogeneous pigmentation pattern. Non-surgical methods in the treatment of LM may be associated with higher recurrence rates. Melanocytes in LM may not respond to pigment-specific wavelengths due to a loss of pigment production ability [14]. Lasers only damage the superficial skin, creating a scar. This conceals the incompletely destroyed tumour, which might result in unnoticed, deep infiltrative growth of the residual tumour [12]. Niiyama and co-workers assume the possibility of laser influence on the progression from LM to LMM [14]. The possibility of sampling errors might be more likely, as LM tends to be large and invasive foci may be missed due to partial excision.

From a molecular point of view, continuous expansion must be considered immortalization of melanocytes while clonal divergence is a sign of enhanced mutation rate within the melanocyte population which is the prerequisite of further malignant progression. On the other hand, histological changes may be very subtle in LM and not present in all areas of the lesion. Therefore, a facial pigmented lesion which recurs after destructive treatment, as described in case 1, should be considered suspicious of LM as relapse after laser treatment could be a sign of melanocyte immortalization. Likewise, a heterogeneous pigmentation pattern as demonstrated by figure 2A is equally suspicious of LM. Complete excision should be the treatment of choice for achieving accurate microstaging and reducing the likelihood of recurrence in LM [28].

Use of laser therapy in the treatment of pigmented lesions, e.g. lentigines and melanocytic naevi, is common and increases the risk of delayed melanoma diagnosis, thus preventing timely and appropriate therapy. This may lead to a fatal outcome. We believe that this medical problem is underreported. A careful examination of all pigmented lesions using

surface microscopy and representative biopsies in combination with a close follow-up is recommended. The development of melanoma subsequent to laser treatment of histologically documented benign lesions introduces the possibility of melanoma induction by lasers.

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Table

Table 1 Clinical findings in 12 patients.

Patient number	Sex	Age (years)	Initial clinical evaluation	Lesion location	Laser type	Melanoma type	Laser treatment to melanoma diagnosis (months)
1	f	52	Seborrheic keratosis	Cheek	CO ₂ , Erbium	n.c.	80.94
2	m	72	Melanocytic naevus	Forehead	n/a	LMM	20.00
3	m	66	Lentigo	Cheek	CO ₂	LM	84.00
4	f	75	n/a	Praeauricular	CO ₂	LM	n/a
5	f	63	Melanocytic naevus	Mandibular	n/a	SSM	6.41
6	f	46	Melanocytic naevus	Eyebrow	n/a	n/a	9.00
7	m	47	Verruca vulgaris	Praeauricular	CO ₂	NMM	12.20
8	f	21	Melanocytic naevus	Upper arm	n/a	ALM	12.00
9	f	45	Verrucous naevus	Forehead	n/a	NMM	5.75
10	f	59	Lentigo solaris	Cheek	Erbium:YAG	LMM	34.29
11	f	75	Basal cell carcinoma	Upper arm	CO ₂	NMM	18.00
12	f	40	Lentigo maligna	Under lower lip	CO ₂	NMM and ALM	84.00

Abbreviations: f, female; m, male; n/a, not applicable; LMM, lentigo maligna melanoma; ALM, acrolentiginous melanoma; LM, lentigo maligna; SSM, superficial spreading melanoma; NMM, nodular malignant melanoma; n.c., not classifiable; YAG, Yttrium-aluminium-garnet; CO₂, carbon dioxide.

Legends for figures

Fig. 1. Hematoxylin and eosin stained histological sample from patient 1 after the third laser treatment, in overview (A) and detail (B): focal pigmented junctional melanocytic naevus. Melanoma at point of diagnosis six years after first laser treatment, three years after naevus excision, in overview (C) and detail (D).

Fig. 2. (A) Lesion on the forehead of patient 2 prior to sample excision and laser treatment. (B) Biopsy prior to laser treatment, already showing limited sample size and quality. (C) Lesion in detail showing atypical naevus over actinically damaged skin considered as melanoma *in situ*. Melanoma with dermal satellite metastases (arrow) two years after laser treatment (D).